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REMARKS

The Invention

The invention features methods for making biomaterials by polymerizing two or more precursor components via a Michael-type reaction of a strong nucleophile and a conjugated unsaturated bond.

Support for the Amendments

The Sequence Listing and claim 8 have been amended to correct typographical errors, and the SEQ ID NOs in the specification have been amended to conform with the amended Sequence Listing. No new matter has been added by any of these amendments.

The Office Action

Claims 1-19 are pending. Poly(ethylene glycol) dithiol and poly(ethylene glycol) tetraacrylate are the elected species. Claims 1-19 stand rejected for obviousness in view of Hubbell et al. (U.S. Patent No. 5,573,934; hereafter "Hubbell").

Rejections under 35 U.S.C. § 103(a)

Claims 1-19 are rejected for obviousness in view of Hubbell. M.P.E.P. § 2143 states:

> To establish a *prima facie* case of obviousness, ... there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings...[, and] the prior art reference... must teach or suggest all the claim limitations.

Applicants assert that this standard has not been met in the present case.

Claim 1, from which claims 2-4, and 6-19 depend, recites:

> 1. A method for making a biomaterial, said method comprising combining two or more precursor components of said biomaterial under conditions that allow polymerization of the two components, wherein *said polymerization occurs through self selective reaction between a strong nucleophile and a conjugated unsaturated bond or a conjugated unsaturated group, by nucleophilic addition*, wherein the functionality of each component is at least two, and wherein said biomaterial does not comprise unprocessed albumin, and said unsaturated bond or group is not a maleimide or a vinyl sulfone. (Emphasis added.)

Independent claim 5 is further limited to a nucleophile that is an amine.

Thus, all of the instant claims are directed to methods of producing a biomaterial through a nucleophilic addition reaction, called the Michael-type reaction, that occurs by the addition of a nucleophile, e.g., a thiol, to a conjugated unsaturated bond or group, e.g., an acrylate group.

In rejecting claims 1-19, the Examiner states:

> [Hubbell] teaches making a material by reacting a strong nucleophile (see Col 6) which is composed of a synthetic polymeric macromer (e.g., PEG), a polymerizable substituent (e.g. polyacrylates) and [an] unsaturated group or bond (see top of col 7). (pg. 2, last paragraph)

This statement is incorrect. Hubbell does not mention, let alone teach or suggest, the use of a strong nucleophile in a polymerization reaction. The list of polymers

on Column 6 of Hubbell is not a list of nucleophiles, but rather a list of hydrophilic backbones that may used in the polymerization reactions described in the reference.

Hubbell does not teach or suggest all the limitations of claims 1-19 because, in contrast to the present invention, Hubbell is directed to methods of coating various substrates through a free radical polymerization process. This process involves the production of radicals by the application of light or heat, which then react with unsaturated bonds to form a cross-linked material. The free radical process of Hubbell is thus chemically distinct from that of the instant claims because the instant claims require the reaction of a strong nucleophile with a conjugated unsaturated bond or group. The distinction is clearly illustrated by the fact that the process of Hubbell requires light or heat in order to initiate polymerization, while the present methods do not require light or heat for polymerization to occur. Although both Hubbell and the instant claims may employ PEG acrylate derivatives, Hubbell's method occurs by a different mechanism and requires starting materials that differ from those recited in the instant claims. Thus, Hubbell does not teach or suggest every limitation present in claims 1-19.

There is no motivation to modify the methods of Hubbell to arrive at the methods of claims 1-19. Regarding motivation, the Examiner states:

> The inventors, [Hubbell] et al., have provided substantial teachings to one of ordinary skill in the art by the time the instant invention was made with their multitude of patents and papers. The

information provided gives the motivation to optimize their materials and guidance to do so. (pg. 3, third paragraph)

As an initial note, it is unclear what patents and papers the Examiner is referring to since only one reference was cited in the last Office Action. Regarding Hubbell, the entire disclosure is directed to methods of producing polymers via free radical polymerization. Hubbell does not suggest anywhere that other methods of polymerization would be suitable or desirable. Hubbell does disclose that free radical polymerization is a way to produce polymers in contact with living cells or tissues in a very short time (Col. 3, ll. 29-31). Since the Hubbell methods work and meet their stated goals, and the reference provides no indication that other approaches are feasible, there is no motivation to modify Hubbell's approach. If the Examiner continues to disagree, evidence supporting this assertion is required. (M.P.E.P. § 2144.03)

In conclusion, since Hubbell does not teach or suggest the limitations of claims 1-19 and there is no motivation of record to modify Hubbell to produce the instantly claimed methods, the rejection for obviousness should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a petition to extend the period for replying for one month, to and including February 3, 2003. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: February 3, 2003

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Version with Markings to Show Changes Made

A marked-up version of the paragraph on page 74, line 24 – page 75, line 15 is as follows:

Analytical C18 HPLC (linear acetonitrile gradient over 0.1% TFA in water) was used to confirm the relative plasmin-stability of GCY-DLys-N-DArg-DCG (SEQ ID NO: 66). The following samples were run: plasmin; GCYKNRDCG (SEQ ID NO: 58); plasmin + GCYKNRDCG (SEQ ID NO: [66]58); GCY-DLys-N-DArg-DCG (SEQ ID NO: 66); and plasmin + GCY-DLys-N-DArg-DCG (SEQ ID NO: 66). Plasmin (micromolar) was present at 1/1000 the concentration of the peptide (millimolar) and hence did not affect overlain absorbance chromatograms. Overlaying the traces (absorbance at 220 nm or 278 nm) of the peptide elutions vs. those of the peptide + plasmin, demonstrated that the most of the GCYKNRDCG (SEQ ID NO: 58)peptide was degraded in approximately 1 hour at 37 C. The GCY-DLys-N-DArg-DCG (SEQ ID NO: 66) peptide however, was unaffected by the plasmin at 24 hours, and remained unaffected over the lifetime of the plasmin in the sample (sample injected for C18 at 2 weeks).

A marked-up version of the paragraph on page 74, line 24 – page 75, line 15 is as follows:

PEG gels were prepared as described above, using the peptide GCGYGRGDSPG (SEQ ID NO: 61). Most cells have receptors that recognize the sequence GRGDSPG (SEQ ID NO: 74), and cells will interact with surfaces displaying immobilized RGD containing peptides. To test cellular interactions of cells with PEG gels containing peptides incorporated via conjugate addition, gels were formed and human umbilical vein endothelial cells were seeded onto the gels. The change in the shape of the cells on the surface was observed, which indicated that the cells were interacting with the peptides on the surface. The change in shape is referred to as spreading, and refers to the change of the cell shape from spherical to flattened and polygonal on the surface. No cell spreading occurred on the PEG gels without peptide, and the specificity of the GCGYGRGDSPG (SEQ ID NO: 61) peptide was confirmed by comparison with gels containing the peptide GCGYGRDGSPG (SEQ ID NO: [61]68), which contains the same amino acids, but in a different sequence, and which has no biological activity. Cells were seeded onto the gels at a concentration of 400 cells per mm^2, and the number of spread cells per area were counted at different times (see Figure 6). The experiments were performed using the normal cell culture medium. Cells could only spread on gels that contained the peptide

GCGYGRGDSPG (SEQ ID NO: 61), which was incorporated into the gels utilizing a conjugate addition reaction.

A marked-up version of the paragraph on page 76, line 20 – page 77, line 1 is as follows:

Microspheres are formed via conjugate addition cross-linking of PEG-triacrylate and the peptide GCYdKNdRDCG (SEQ ID NO: [68]66) as in Example 7, but additionally the peptide GCGYGRGDSPG (SEQ ID NO: 61) is also included in the reaction mixture, at a ratio of 1 GCGYGRGDSPG (SEQ ID NO: 61) to 8 GCYdKNdRDCG (SEQ ID NO: [68]66). The bioactive peptide is tested for the ability to localize microspheres to the surfaces of cells, as compared with microspheres containing no bioactive peptide.

A marked-up version of claim 8 is as follows.

8. (Amended) The method of claim 1, wherein one of said components has a functionality of at least three.